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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,652	10/13/2000	Hai U. Wang	1802.1003-009	6630
21005	7590 03/05/2003			
HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 VIRGINIA ROAD P.O. BOX 9133			EXAMINER	
			ANDRES, JANET L	
CONCORD, MA 01742-9133			ART UNIT	PAPER NUMBER
			1646	
			DATE MAILED: 03/05/2003	

Please find below and/or attached an Office communication concerning this application or proceeding.

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	Application No.	Applicant(s)				
	09/687,652	WANG ET AL.				
Office Action Summary	Examiner	Art Unit				
	Janet L Andres	1646				
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply						
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM						
THE MAILING DATE OF THIS COMMUNICATION. - Extensions of time may be available under the provisions of 37 CFR 1.13 after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply of If NO period for reply is specified above, the maximum statutory period. - Failure to reply within the set or extended period for reply will, by statute, any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).	36(a). In no event, however, may a reply be to within the statutory minimum of thirty (30) da will apply and will expire SIX (6) MONTHS fron cause the application to become ABANDONI	mely filed ys will be considered timely. n the mailing date of this communication. ED (35 U.S.C. § 133).				
Status	December 2001					
1) Responsive to communication(s) filed on 10 E						
,	is action is non-final.	prosecution as to the merits is				
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11, 453 O.G. 213. Disposition of Claims						
4) Claim(s) 46,47,49,50,77-89,92,93,95-100,107	,108,114,120 and 151-157 is/are	e pending in the application.				
4a) Of the above claim(s) is/are withdraw						
5)⊠ Claim(s) <u>151</u> is/are allowed.						
6)⊠ Claim(s) <u>46,47,49,50,77-86,88,89,92,95-100,107,108,114,120 and 152-155</u> is/are rejected.						
7)⊠ Claim(s) <u>93,156 and 157</u> is/are objected to.						
8) Claim(s) are subject to restriction and/or election requirement.						
Application Papers						
9)☐ The specification is objected to by the Examiner.						
10) The drawing(s) filed on is/are: a) accepted or b) objected to by the Examiner.						
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).						
11) The proposed drawing correction filed on is: a) approved b) disapproved by the Examiner.						
If approved, corrected drawings are required in reply to this Office action.						
12) The oath or declaration is objected to by the Examiner.						
Priority under 35 U.S.C. §§ 119 and 120						
13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).						
a) All b) Some * c) None of:						
	 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 					
2. Certified copies of the priority documents have been received in Application No3. Copies of the certified copies of the priority documents have been received in this National Stage						
application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received.						
14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).						
a) ☐ The translation of the foreign language provisional application has been received. 15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.						
Attachment(s)						
 Notice of References Cited (PTO-892) Notice of Draftsperson's Patent Drawing Review (PTO-948) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1 	5) Notice of Informa	ary (PTO-413) Paper No(s) I Patent Application (PTO-152)				
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RESPONSE TO AMENDMENT

1. Applicant's amendment filed 10 December 2002 is acknowledged. Claims 46, 47, 49, 50, 77-89, 92, 93, 95-100, 107, 108, 114, 120, and 151-157 are pending and under examination in this application. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claim Rejections/Objections Withdrawn

2. The rejection of claims 45 and 77-87 under 35 U.S.C. 112, first paragraph, as lacking enablement for portions is withdrawn in response to Applicant's arguments. The rejection of claims 48-50 and 114-150 under 35 U.S.C. 112, fist paragraph, as lacking enablement because enhancers of interaction could not predictably be identified is withdrawn because activators such as co-receptors are known in the art and could be identified by such screens.

New Grounds of Rejection

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
- 4. Claims 46, 49, 77-82, 84, 85, 114, 120, and 153 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. patent 6,514,497 (Briskin et al., 2003, priority date 1997).

The '497 patent teaches in column 5, lines 44-47, that LERK-2 binds to the Eph receptors Cek10, Sek-4, Tyro6, Hek2, Cek5, Nuk, Tyro5, Erk, Cek6, and Elk. LERK2 is an ephrin B1. (It is identified as ephrin B2 in column 17, lines 47 of the '497 patent; this appears to be an error.)

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The receptors are EphB1, Eph B2, and EphB3 receptors. See The Eph Nomenclature Committee, Cell, 1997, vol. 90, pp. 403-404, particularly table 1 on p. 404. That interaction of LERK-2 with its receptors results in angiogenesis is taught in column 4, lines 3-20. The '497 patent teaches assays for inhibitors and promoters of LERK-2 mediated cell adhesion in column 9, lines 59-67 and column 10, lines 1-20. Monitoring angiogenesis as a method of detection is taught in column 10, lines 5-12, thus anticipating the limitations of claims 46 and 49. That Applicant's method includes the mental step of selecting the receptor and ligand based on cell expression does not change the method itself. The resulting method uses the same ligand and the same receptors for the same purpose. The use of soluble molecules is taught in column 10, lines 42-57, anticipating the limitations of claim 77. Use of a radiolabel is taught in the same lines, anticipating the limitations of claims 78 and 79. Antibodies, which are polypeptides and organic molecules, are taught in column 10, lines 20-29, anticipating the limitations of claims 80 and 81. Further, the nature of the compound identified would not change the method. Cell surface expression is taught in column 9, lines 59-67, anticipating the limitations of claim 82. As stated above, the mental step of selecting the ligand or receptor on the basis of expression, as claimed in claim 84, does not change the method itself. Thus claim 84 is also anticipated by the '497 patent. The genetic modification of claim 85 is taught in column 12, lines 26-33. Contacting of a soluble molecule with a cell-surface one is taught in column 10, lines 42-57, anticipating the limitations of claim 120. Cultured cells are taught in column 9, lines 59-67, anticipating the limitations of claim 153.

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5. Claims 47, 50, 80, 81, 88, 89, 92, 95-100, 107, 108, and 152 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. patent 6,413,730 (Holland et al., 2002, priority date 1996).

The '730 patent teaches that hHtk-L/ELF-2/LERK5 is a ligand for Elk related kinases in column 5, line 34. The '730 patent further teaches that the receptors for this ligand include Htk and its mouse homologue Myk1. hHtk-L/ELF-2/LERK5 is the molecule now known as ephrin B2. Htk and Myk1 are now known as eph B4. See The Eph Nomenclature Committee, cited above. Thus, the '730 patent teaches ephrin B2 as a ligand for Eph B4. Methods for identifying inhibitors and activators of the interaction of receptor and ligand, as claimed in instant claims 47 and 50, are taught in column 2, lines 11-34 and claimed in claims 1 and 5. That such agents could be polypeptides such as antibodies, as claimed in instant claims 80 and 81 is taught in column 3, lines 47-55. As stated above, antibodies are organic molecules. That the effectors identified could be natural or synthetic drugs is taught in column 8, lines 13-16. Further, as stated above, the nature of the molecule identified would not alter the method. Detectable labels, as claimed in claims 88 and 89, are taught in column 9, lines 1-5, in which tyrosine phosphorylation is indicated as a method of detection. Cell expression, as claimed in claim 92, is taught in column 2, lines 16-25. Recombinant expression, as claimed in claim 95, is taught in column 8, lines 32-40. Solid supports, as claimed in claims 96 and 97, are taught in column 8, lines 55-57; diffusible proteins are taught throughout; see column 2, for example. Fusion proteins, as claimed in claims 98-100, are taught in column 7, lines 23-39. That the receptor may be soluble is taught throughout, as set forth above; that the ligand may be bound to the cell is taught in column 8, lines 33-37, thus anticipating the limitations of claim 107. That the ligand

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may be soluble is taught in column 8, lines 37-40 of column 8 and that the receptor may be expressed on cells is taught in column 7, lines 34-39, thus anticipating the limitations of claim 108. Expression on cultured cells is taught in column 8, lines 32-40, anticipating the limitations of claim 152.

- 6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
 - (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- 7. Claim 83 is rejected under 35 U.S.C. 103(a) as being unpatentable over the '497 patent in view of Pandey et al., Science, 1996, vol. 268, pp. 567-569.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

- 1. Determining the scope and contents of the prior art.
- 2. Ascertaining the differences between the prior art and the claims at issue.
- 3. Resolving the level of ordinary skill in the pertinent art.
- 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The '497 patent teaches as set forth above but fails to teach expression on isolated arterial or venous cells as claimed in claim 83. Pandey et al. teaches that B61, which is ephrin A1, activates Eck, which is EphA2 (see Eph Nomenclature Committee, above), on human umbilical cord venous cells (HUVECs) (p. 568). Pandey et al. additionally teaches that B61 is angiogenic (figure 2, p. 568). Pandey et al. fails to teach HUVECs for use in assays for effectors, as

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instantly claimed. However, it would be obvious to one of ordinary skill in the art to combine the teachings of the '497 patent with those of Pandey et al. to use such a system to assay for effectors, since one of ordinary skill would expect such an assay to be useful for identifying modulators of ephrin A1/EphA2 interaction, and would expect such modulators to affect angiogenesis.

8. Claim 86 is rejected under 35 U.S.C. 103(a) as being unpatentable over the '497 patent in view of the '730 patent.

The '497 patent teaches as set forth above, but fails to teach the use of solid supports as claimed in claim 86. The '730 patent teaches solid supports in column 8, lines 55-57, but fails to teach the angiogenic assays of the '497 patent. However, it would be obvious to one of ordinary skill in the art to combine the teachings of the '730 patent with those of the '497 patent to arrive at the invention of claim 86. One of ordinary skill would have been motivated to do so because the '730 patent teaches that this is a useful assay system and one of ordinary skill would thus expect that the modification of the assays of the '497 patent to use solid supports would similarly be useful.

9. Claims 154 and 155 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '497 patent.

The '497 patent teaches as set forth above but fails to explicitly teach further assessment of inhibitors identified by the method of claim 46 *in vivo* or *in vitro*. However, it would be *prima facie* obvious to one of ordinary skill in the art to further evaluate such inhibitors by further testing in *in vivo* and *in vitro* systems. One of ordinary skill would be motivated to do so because the '497 patent teaches therapeutic uses in column 13, lines 8-34 but teaches in column

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14, lines 81-61, that testing beyond the described assays is required. One of ordinary skill would thus expect that the inhibitors identified by the methods of claim 46 would have therapeutic use, but would know that testing would be required in order to assess the compounds for therapeutic effect.

10. Applicant is advised that should claim 46 or 49 be found allowable, claim 86 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 93 is objected to as depending from a rejected claim but is otherwise allowable.

Claims 156 and 157 are objected to because "comprising" appears to have been omitted after "activity".

CLAIMS 46, 47, 49, 50, 77-86, 88, 89, 92, 95-100, 107, 108, 114, 120, AND 152-155 ARE REJECTED. CLAIMS 93, 156, AND 157 ARE OBJECTED TO. CLAIM 151 IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

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Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [yvonne.eyler@uspto.gov].

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D. Patent Examiner

March 4, 2003